Prenatal Exposures and Schizophrenia

Hypothesis submitted to NCS Study Design Working Group and Federal Advisory Committee

I. Hypothesis

Converging evidence suggests that many cases of schizophrenia are neurodevelopmental in origin, and that both genes and environment play a role in the etiology of these cases. Exposures in early gestation have been linked to schizophrenia, in particular, infection and nutritional deficiency (e.g., see Cannon et al., 2002; Susser et al., 1999). There is also suggestive evidence for maternal stress (bereavement and war) and chemical exposure (lead). Some of these associations have been reported in studies with excellent prenatal data, including serum samples . None of the findings, however, are definitive, primarily due to small numbers.

In this context, we propose:

- To study associations between a selected group of prenatal exposures and schizophrenia. The exposures are chosen based on the existence of both prior evidence of an association with schizophrenia, and biological plausibility. We will initially focus on prenatal viral infections (e.g., rubella, HSV and influenza have been associated with schizophrenia) and key micronutritients (e.g., folate and vitamin A). The investigation will then extend to other potential risk factors including maternal stress and chemical exposures.

- To illuminate gene-environment interactions by examining whether these prenatal exposures have different effects in individuals with varying degrees of genetic susceptibility to schizophrenia. At present, a reasonable indicator of genetic liability is having a first degree relative with schizophrenia. But it is likely that within 20-30 years, we will have identified one or more specific alleles that confer increased risk of schizophrenia, in which case these alleles will be used to indicate genetic liability.

- To examine the interaction between prenatal exposures and advanced paternal age at birth. Paternal age >40years has been associated with a high risk of schizophrenia in several birth cohort studies (e.g., Malaspina et al., 2001), and this association is often presumed though not proven to reflect de novo mutations. Thus the study of this interaction may provide a further means to illuminate gene-environment interaction in schizophrenia.

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III. Public Health Significance

Schizophrenia is a severe psychiatric disease typically appearing in late adolescence or early adulthood. It is associated with significant long-term morbidity, occupational disability, social disadvantage, and high mortality from suicide and other causes. The burden of the disease extends to the family, for whom there are major economic and social implications. The prevalence of schizophrenia is approximately 1%, but as a chronic disabling condition schizophrenia absorbs a significant proportion of public health, and social welfare and economic resources (Wyatt et al., 1995). A more secure understanding of relevant prenatal environmental (i.e., infection, nutrition) exposures will lay the foundation for prevention efforts, aimed at reducing vulnerability to this disease.

IV. Justification for a Large, Prospective Longitudinal Study

Investigation of the prenatal origins of schizophrenia requires a large prospective cohort that has been followed from early gestation up to adulthood. Among the reasons are:

- A *prospective* study is required to obtain precise prenatal exposure data. For the exposures of interest --- e.g., prenatal infection—biological specimens are essential to precise measurement. Serum and placental specimens can, however, be collected prospectively but stored for later analysis. To conserve specimens and reduce cost, we would employ a *nested case control* design.

- The *longitudinal* design is also required because it is important to trace the development of the cohort through childhood and adolescence, before the onset of schizophrenia. Several reports from smaller cohorts have indicated childhood antecedents (or perhaps risk factors) that can predate formal diagnosis by decades (Cannon et al., 2002). In addition, while prenatal exposures may play an important role in schizophrenia, this by no means precludes an important role for postnatal experience. Indeed, some reports have suggested that adverse childhood experiences contribute to increased risk of schizophrenia.

- A *large cohort* is required to study this relatively infrequent outcome. As noted above, earlier studies with good prenatal data have suggested relationships of prenatal exposures to the outcome of schizophrenia, but their interpretation is limited by small numbers.

- A *large cohort* is virtually a precondition for extending this field to investigate gene-environment interactions.

V. Scientific Merit

The “neurodevelopmental theory” proposes that schizophrenia has its origins in prenatal brain development. The theory has been supported by evidence from several types of human and animal studies (Susser et al., 1999), and is presently the prevailing view among schizophrenia researchers. Findings in patients with schizophrenia that suggest early origins include minor physical anomalies, developmental disturbances in childhood, and specific structural anomalies on brain imaging. By the time of onset schizophrenia is associated with ventricular enlargement and decreased hippocampal volume, and these may possibly also have early origins; these findings are evident in discordant monozygotic twins, suggesting they are partly of environmental origin. Nonetheless, we still lack any definitive evidence of a prenatal exposure that increases risk of schizophrenia. By providing such evidence, (or refuting the hypothesis),

the NCS will contribute in a unique and fundamental way to our understanding of the causes of schizophrenia.

VI. Potential for Innovative Research

The technologies used in the direct and indirect assessment of relevant prenatal exposures will include serologic analyses and placental pathology. These methods, which are common to many of the research hypotheses addressed in the NCS, are exceptionally useful in the context of the present hypothesis. Each provides a window on gestational experience, and holds the potential to improve our knowledge of the identity, timing, and mechanisms of exposures adversely influencing neurodevelopment and elevating risk of schizophrenia.

- Serum Samples. In addition to basic serologic analyses for specific infections (e.g., influenza, HSVII), high throughput methods will be used to detect and quantitate viral nucleic acids, antiviral antibodies, and host factors. This will permit the simultaneous measurement of multiple analytes, using small amounts of sera.

- Placenta. Placental data can be used to indicate nutritional, infectious, toxic and other exposures. Novel technologies of digital image capture for gross assessment of placenta and image analysis will standardize gross measures, and extend what can be measured in the placenta. The development of a rigorous placental histology assessment tool, proposed in a separate pilot study, will amplify the information available by identifying major pathology types (e.g., acute inflammation, chronic inflammation and vascular pathology). These advances will permit us to assess potential mechanisms for the influence of adverse exposures reflected in the placenta.

- Ultrasound. We anticipate that the NCS will utilize 3-D ultrasound in utero and in infancy, for the first time in a large cohort, providing an image of brain development relevant to the proposed project.

Taken together these three measures will provide unprecedented access to early gestational life, and go directly to the core of the *neurodevelopmental hypothesis*.

VII. Feasibility

VIIa. Critical Period for Exposures and Outcomes.

Our central interest is in prenatal development. *Early gestation* is a time of unique vulnerability to the consequences of environmental insult. There is evidence for both infectious and nutritional exposures during this period profoundly affecting brain development. From the perspective of exposure measurement, early gestation is therefore of crucial interest in the work proposed here.

From the perspective of outcome, we are interested in childhood markers of and risk factors for schizophrenia, and would therefore propose that specific postnatal assessments be periodically conducted during childhood and adolescence. Interest lies in the trajectory of cognitive development, language development, motor development, sensory development, psychological and social development as well as the appearance of specific psychiatric symptoms over time. Outcome ascertainment should begin at 21 years, at which point about approximately 30% of cases will have emerged (Jablensky et al., 1992). This would permit preliminary assessment of early onset cases. Cases should again be sought at ages 30 and finally at age 40 when about 90% of the cases will have emerged.

VIIb. Sampling Needs

VIIbi. Subgroups. The study of gene-environment interaction will be enhanced by the identification of high risk subgroups who have a genetic susceptibility to schizophrenia. At present these are best defined by having a first degree relative with schizophrenia, or by having a biological father >40years at time of birth. The identification of the high risk individual will not automatically lead to more detailed assessments in these groups.

VIIbii. Power. Although we plan nested case control studies, for simplicity we present power for the entire cohort. The use of placental data and serum from early gestation (preferably first trimester) will reduce the effective sample size; thus we assume 80,000 subjects with complete measures. We assume that the lifetime risk of the outcome is .01 (this risk will vary according to narrow or broad definitions of schizophrenia and schizophrenia spectrum disorders). For the present purposes, we have assessed the smallest detectable risk , varying the disease probability in the unexposed (appropriate to ascertainment at varying ages), and prevalence of exposure (dichotomized). The smallest detectable risks for a sample size of 80,000 under a range of assumptions is shown below.

SMALLEST DETECTABLE Relative Risk

Probability of Disease in Unexposed	Prevalence Exposure .05	Prevalence of Exposure .10	Prevalence Exposure .20
.003 (Age 21)	RR = 1.9	RR = 1.6	RR = 1.4
.005 (Age 30)	RR = 1.7	RR = 1.5	RR = 1.3
.009 (Age 40)	RR = 1.5	RR = 1.3	RR = 1.2

Assumptions: Power 80%, alpha=.05, Sample Size 80,000

VIIc. Contact

Because we would like to use the entire sample in analyses, information crucial to testing hypotheses will be sought on all members of the cohort.

Cases will be identified among cohort members by first eliciting psychiatric treatment history. Those identified with psychiatric hospitalization, specific pharmacologic treatments or specific diagnoses with a high index of suspicion will be contacted. Face-to-face diagnostic interviews will be conducted on probable cases. This method of screening has been used in several large cohort studies, and has been shown to be effective in identifying possible cases. Only a few questions are required to obtain the information necessary for screening. Screening questions should be administered in adolescence, at 20years, and any subsequent follow-up.

VIId. Measurement Tools

Exposure measurement. The crucial exposure measures involve maternal and paternal questionnaire data, serologic analyses, placental pathology assessment, and 3-D ultrasound (see above).

Outcome measurement. Standardized diagnostic instruments (e.g., the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994)) and symptom scales (e.g., SANS, SAPS, SDS) will be administered in a face-to-face diagnostic interview. These instruments have been extensively tested. One must consider the possibility that in thirty years, however, the state of the art diagnostic interview will require use of an instrument that has not yet been developed.

VIIe. Community Involvement

In the past decade advocacy groups have had an extremely important role in promoting schizophrenia research and reducing the stigma associated with this illness. The most powerful advocacy groups are comprised mainly of close relatives of individuals with schizophrenia (e.g., National Alliance for the Mentally Ill). We believe it is appropriate to involve these and other advocates as advisors to the research program.

VIIf. Other burden to participant and family associated with this hypothesis, not covered above.

The hypothesis, if true, will in all probability reduce the stigma associated with schizophrenia. The burden of stigma extends to genetic relatives of individuals suffering with the disease. It is important to be sensitive, however, to the deep anxieties raised by research on prenatal factors; many mothers wonder whether their actions contributed to the illness of their child. The way in which research programs and ultimately findings are presented can do much to preempt such misunderstandings (advocates are helpful in this respect; see above).

The burden of participation will fall on the family over a very long period of time, inasmuch as the continued participation of parents of cases may be required even when the cohort members are adults

VIII. Collaboration with other Workgroups

This project will involve extensive collaboration with several working groups who clearly share common interests and ends. The groups with the greatest overlap exposures and measures, indeed groups in which the very hypotheses proposed here could be supported, are:

- The Fertility and Early Pregnancy Working Group: peri-conceptional and early gestational exposures; measures of maternal/paternal characteristics and early gestational exposures.

- Pregnancy and the Infant Working Group: maternal, fetal and infant characteristics, conditions and disease states including prenatal infection/inflammation, endocrine and immune disruption, maternal nutrition during pregnancy; measures serial sonograms, maternal serums (urine salvia and blood samples, and hair samples), amniotic fluid, and infection screening for HBB/HCV/HIV .

- Development and Behavior Working Group: gestational exposures including nutrition and chemical exposures; measures of nutritional status of the mother, lead exposure, infant and child behavior and development.

- Gene-Environment Interactions Working Group, Exposures to Chemical Agents Working Group, and Immunity, Infections and Vaccines Working Group.

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